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ORIGINAL ARTICLE

Noninvasive Capnometry for End-tidal Carbon Dioxide Monitoring via Nasal Cannula in Nonintubated Neonates

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Background: Arterial blood gas analysis is the gold standard for assessing the adequacy of ventilation. However, arterial blood sampling may be associated with serious complications in neonates. The aim of the study was to utilize the side-stream capnometry measurement of end-tidal carbon dioxide ($PetCO_2$) via nasal cannula circuits and to verify the reliability of $PetCO_2$ in reflecting the arterial blood carbon dioxide ($PaCO_2$) level in nonintubated neonates.
Methods: A retrospective medical record review analysis was performed in nonintubated neonates admitted to the neonatal ward in a medical center. Simultaneous arterial $PaCO_2$ and $PetCO_2$ levels were evaluated. $PaCO_2$ and $PetCO_2$ levels were compared by paired *t* test and were correlated using Pearson's correlation. The $PetCO_2$ bias was defined as the difference between $PaCO_2$ and $PetCO_2$, and was assessed by Bland-Altman plot analysis.
Results: A total of 34 neonates were recruited, and data of 54 pairs of $PaCO_2$ and $PetCO_2$ levels were available for comparison. The average (mean±SD) gestational age was 32.5±4.2 weeks, and the average birth weight was 1881±1077 g. There was a good correlation between $PetCO_2$ and $PaCO_2$ levels among all paired samples ($r=0.809$, $p<0.001$). When the data were divided into those with respiratory disease ($n=34$) and those without ($n=20$), significant correlation between $PetCO_2$ and $PaCO_2$ levels were both noted in the former group ($r=0.823$, $p<0.001$) and the latter group ($r=0.770$, $p<0.001$). The overall average mean value of $PetCO_2$ was lower than that of $PaCO_2$ (39.4±8.8 mmHg *vs.* 41.3±9.2 mmHg, $p=0.014$). The difference between $PetCO_2$ and $PaCO_2$ levels was significant only among those with respiratory disease (38.8±9.8 mmHg *vs.* 41.2±10.3 mmHg, $p=0.027$), but not among those without (40.5±7.0 mmHg *vs.* 41.6±7.2 mmHg, $p=0.289$).
Conclusions: End-tidal CO_2 measurement by side-stream capnometry through nasal cannula could provide an accurate and noninvasive estimate of $PaCO_2$ levels in nonintubated neonates.

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1. Introduction

The implementation of assisted ventilation for critically ill neonates requires careful attention to the balance between respiratory support and the patient's needs, such as oxygen, tidal volume, and transpulmonary pressure supplied, not to mention the potential complications.[1] Arterial blood gas analysis is the gold standard for assessing the adequacy of ventilation, providing important information on oxygen delivery and carbon dioxide control in the blood. However, these techniques are invasive and in some occasions associated with serious complications such as pain, infection, arterial spasm, and ischemic necrosis in neonates. The advancement in transcutaneous pulse oximetry provides an accurate and noninvasive monitoring of oxygenation, detecting hypoxemia before any serious clinical complications take place in the neonates.[2–4]

The need to efficiently evaluate the level of response to the dynamic changes of CO_2 pressures in neonates has become more important,[5] the reason being that having an overly high or low arterial blood carbon dioxide ($PaCO_2$) level, even for a brief period of time, has been attributed to long-term morbidity. High $PaCO_2$ level may increase cerebral blood flow and the risk of developing intraventricular hemorrhage,[6,7] while hypocarbia may increase the incidence of periventricular leukomalacia and bronchopulmonary dysplasia in critically ill neonates.[8,9] Combined together with pulse oximetry, the measurement of $PaCO_2$ provides an effective and reliable approach to continuously monitor the adequacy of both oxygenation and ventilation in ventilated neonates. Capillary blood sampling and transcutaneous monitoring are two available alternatives for measuring $PaCO_2$.[10] However, capillary blood sampling is invasive and painful, while transcutaneous CO_2 monitoring, which is easily interfered by hypoxia and acidosis, is not well tolerated in small babies with fragile skin.[11,12]

Capnometry is a novel and noninvasive technology that can be used to verify endotracheal tube position during mechanical ventilation and cardiopulmonary resuscitation.[13] There are previous studies providing good estimation of $PaCO_2$ by capnometry in intubated neonates.[14,15] Nevertheless, for nonintubated neonates, capnometry is not applicable because of the lack of a suitable circuit to directly connect to the individual for measuring the volume of exhaled air. In adult studies, Bowe et al[16] and Liu et al[17] reported that noninvasive measurement of end-tidal carbon dioxide level ($PetCO_2$) by infrared capnometry via nasal cannula may provide a good approximation of $PaCO_2$ in nonintubated patients. Using the same technique, Campbell et al[18] and Tobias et al[19] also demonstrated that $PetCO_2$ measurement could be a useful index for assessing the adequacy of ventilation in pediatric patients during the perioperative period. Furthermore, accurate estimation of $PaCO_2$ can also be obtained by noninvasive monitoring of $PetCO_2$ via nasal cannula in spontaneously breathing infants and children during events of hypocarbia, diabetic acidosis, and seizure.[20–22] However, there is very little information concerning the adequacy of this kind of end-tidal carbon dioxide measurement in nonintubated neonates.

This study aimed to determine whether $PetCO_2$ measurement by capnometry via nasal cannula could reliably reflect $PaCO_2$ in nonintubated neonates admitted in neonatal ward.

2. Materials and Methods

This was a retrospective review and analysis of medical records. The study was approved by the Institutional Review Board of National Taiwan University Hospital, which waived the need for informed consent. From July 2004 to January 2005, measurements of arterial $PaCO_2$ and $PetCO_2$ levels by side-stream capnometry via nasal cannula in nonintubated neonates admitted to the neonatal ward were selected for analysis. Patients with congenital heart disease were excluded.

Exhaled CO_2 volume was measured using an infrared analyzer capnometer (CO_2SMO Plus! Model 8000; Novametrix Medical System Inc., Wallingford, CT, USA), which had a dead space smaller than 1 mL and a response time less than 60 milliseconds. The nasal sampling cannula (Nasal sampling cannula-Pediatric; Novametrix Medical System Inc.) was connected to the sampling adaptor with the CAPNOSTAT CO_2 sensor (Cat. No. 5843; Novametrix Medical System Inc.), and the cannula tip was inserted into the nostrils of the patient. Arterial blood gas obtained from indwelling arterial catheters was analyzed by Automatic Blood Gas (Nova Biomedical, Stat 5 Profile; Nova Biomedical Co., Waltham, MA, USA), which was calibrated on a daily basis. Arterial blood gas was generally obtained 30 minutes after chest care, and exhaled carbon dioxide volume was measured simultaneously. Heart rate, respiratory rate, and transcutaneous oxygen saturation level were also routinely recorded.

All data were analyzed using the SPSS (version 11.5; SPSS Inc., Chicago, IL, USA). Differences between $PaCO_2$ and $PetCO_2$ measured for all enrolled patients were compared by paired *t* test. The precision of the noninvasive technique, and the agreement comparing the results with $PaCO_2$, were assessed by $PetCO_2$ bias, which was defined as $PaCO_2$ minus $PetCO_2$. Bland-Altman analysis was used to determine

the precision and the bias.[23,24] The Bland-Altman plot was drawn by MedCalc (version 7.5.0.0; MedCalc Software, Belgium). $PaCO_2$ and $PetCO_2$ were correlated using Pearson's correlation coefficient and linear regression analysis. A statistically significant difference was defined as p value <0.05.

3. Results

A total of 34 patients (18 males and 16 females; 13 term infants and 21 preterm infants) were recruited, and 54 pairs of $PaCO_2$ and $PetCO_2$ samples were compared. The average gestational age of these patients was 32.5±4.2 weeks (range: 25–40 weeks), and the average birth body weight was 1881±1077 g (range: 630–4450 g). The diagnosis of respiratory disease was made in 19 patients, including those with transient tachypnea of neonate, perinatal aspiration syndrome, neonatal pneumonia, and other symptoms. No significant complications were observed in the course of $PetCO_2$ monitoring.

The $PetCO_2$ biases (95% CI), defined as $PaCO_2$ minus $PetCO_2$, among the preterm group, full term group, respiratory disease group, and nonrespiratory disease group were 1.8±6.0 mmHg (−0.2 to 3.8 mmHg), 2.3±4.8 mmHg (−0.2 to 4.8 mmHg), 2.4±6.0 mmHg (0.3 to 4.5 mmHg), and 1.2±4.8 mmHg (−1.1 to 3.4 mmHg), respectively. The Bland-Altman plot of the difference between the $PetCO_2$ bias and the average of $PaCO_2$ and $PetCO_2$ levels as well as the linear regression curve of $PaCO_2$ and $PetCO_2$ levels among all paired samples and different groups classified by respiratory disease are shown in the figures (Figures 1–3). There was a good correlation between $PetCO_2$ and $PaCO_2$ among all paired samples ($n=54$, $r=0.809$, $p<0.001$; Figure 1B), and the correlation between $PetCO_2$ and $PaCO_2$ was also significant among patients with respiratory disease ($n=34$, $r=0.823$, $p<0.001$) and those without ($n=20$, $r=0.770$, $p<0.001$; Figures 2B and 3B).

The overall average (mean±SD) $PetCO_2$ values were significantly different from the $PaCO_2$ values in 54 paired samples ($PetCO_2$=39.4±8.8 mmHg *vs.* $PaCO_2$=41.3±9.2 mmHg, $p=0.014$). When the $PetCO_2$ values were further divided according to preterm ($PetCO_2$=39.5±9.3 mmHg *vs.* $PaCO_2$=41.2±9.6 mmHg, $p=0.079$, $n=37$) and term ($PetCO_2$=39.3±8.0 mmHg *vs.* $PaCO_2$=41.6±8.5 mmHg, $p=0.065$, $n=17$), there were no significant differences. However, when comparing the results based on whether the patients had respiratory disease or not, there was a statistically significant difference between $PetCO_2$ and $PaCO_2$ in the respiratory disease group ($PetCO_2$=38.8±9.8 mmHg *vs.* $PaCO_2$=41.2±10.3 mmHg, $p=0.027$, $n=34$), whereas the group without respiratory disease had no difference ($PetCO_2$=40.5±7.0 mmHg *vs.* $PaCO_2$=41.6±7.2 mmHg, $p=0.289$, $n=20$).

4. Discussion

Carbon dioxide is a product of cellular metabolism in the tissues, and is transported to the right heart via the venous system. Then, it is pumped into the lungs by the heart, and diffuses out into the exhaled air. Continuous capnometry monitors exhaled CO_2 levels noninvasively and provides important clinical information for the assessment of ventilation, perfusion, and systemic metabolism.[25,26] Monitoring of end-tidal CO_2 by capnometry in intubated patients has already become widely used. For nonintubated patients, the degree of clinical usefulness of $PetCO_2$ monitoring has also improved after the development of side-stream circuits and nasal sampling apparatus.[27–29] The results from previous

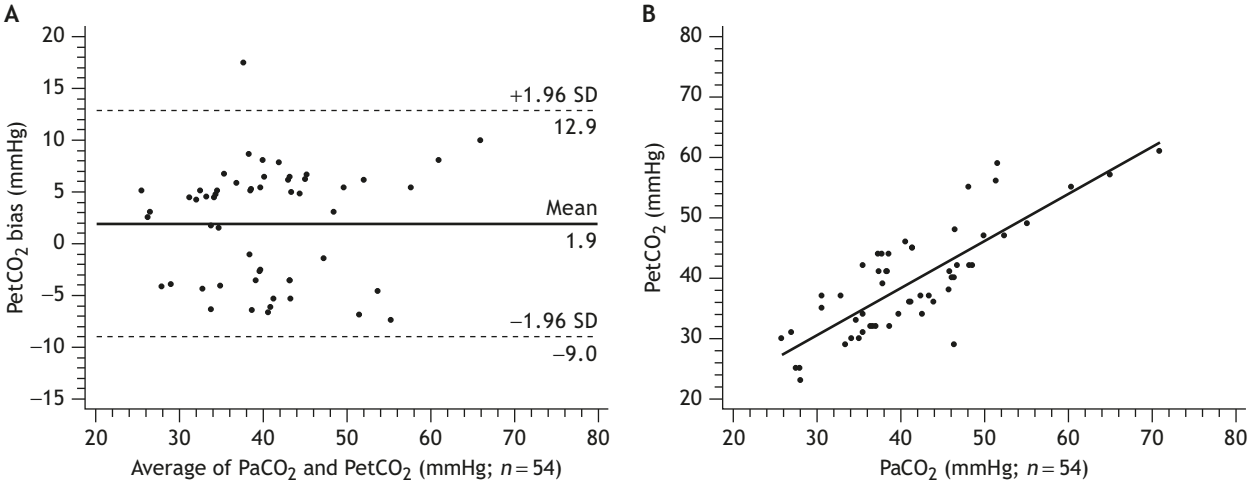

Figure 1 (A) Bland-Altman plot of difference between $PetCO_2$ bias ($PaCO_2$ − $PetCO_2$) and the average of $PaCO_2$ and $PetCO_2$ [($PaCO_2$+$PetCO_2$)/2] for all neonates. (B) Linear regression of $PaCO_2$ and $PetCO_2$ for all neonates.

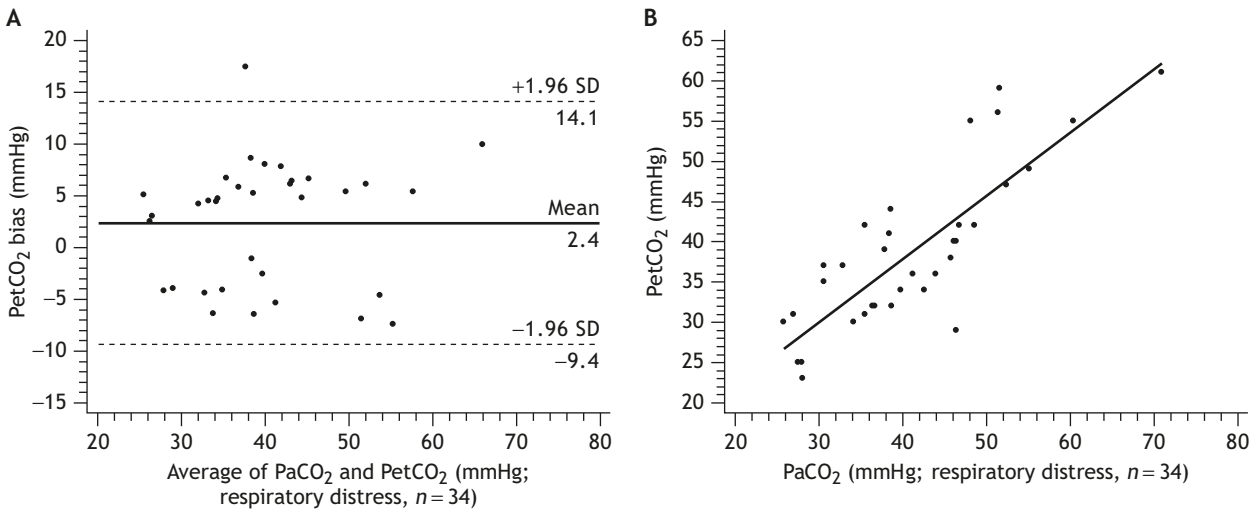

Figure 2 (A) Bland-Altman plot of difference between $PetCO_2$ bias ($PaCO_2 - PetCO_2$) and the average of $PaCO_2$ and $PetCO_2$ [$(PaCO_2 + PetCO_2)/2$] for neonates with respiratory disease. (B) Linear regression of $PaCO_2$ and $PetCO_2$ for neonates with respiratory disease.

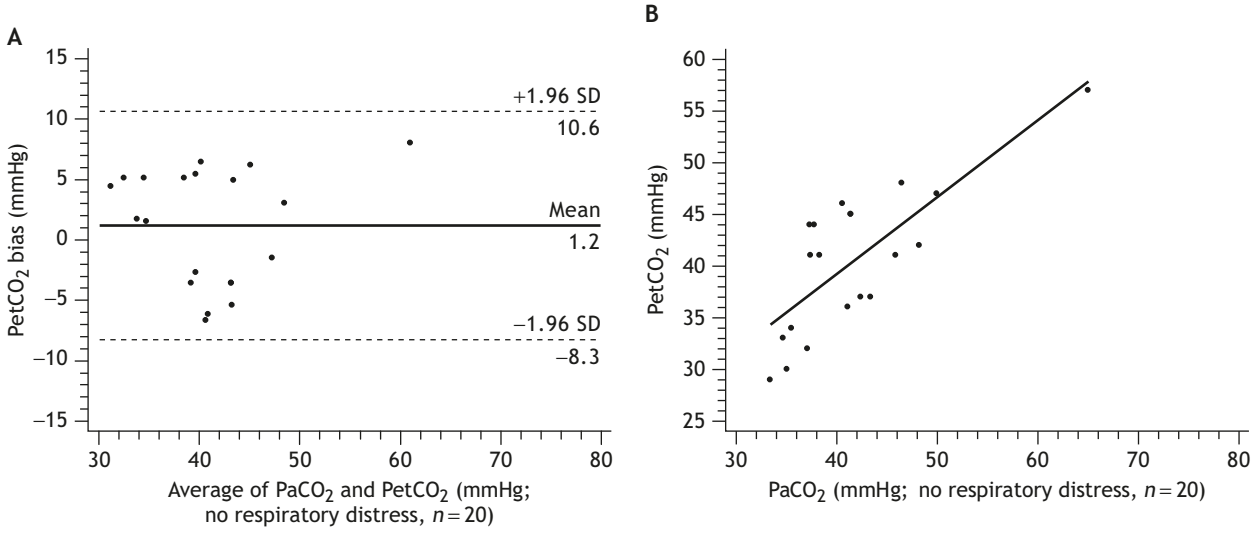

Figure 3 (A) Bland-Altman plot of difference between $PetCO_2$ bias ($PaCO_2 - PetCO_2$) and the average of $PaCO_2$ and $PetCO_2$ [$(PaCO_2 + PetCO_2)/2$] for neonates without respiratory disease. (B) Linear regression of $PaCO_2$ and $PetCO_2$ for neonates without respiratory disease.

studies suggest that noninvasive monitoring of $PetCO_2$ levels measured via nasal cannula may provide a clinically useful approximation of $PaCO_2$ in nonintubated pediatric patients.[18–22] The application of noninvasive capnometry is essential in neonates who are not intubated but still in a vulnerable period requiring close monitoring. Accordingly, we used the side-stream capnometry method via a special pediatric nasal cannula to measure $PetCO_2$ levels in nonintubated neonates. In this study, we demonstrated that end-tidal CO_2 levels measured via nasal cannula do reflect the arterial CO_2 levels in these nonintubated neonates.

The reading and trend results of $PetCO_2$ should be interpreted with caution. The presence of exhaled CO_2 entails cardiopulmonary function and tissue perfusion. Several factors may contribute to the inaccuracy of $PetCO_2$ monitoring. Sampling errors may occur in patients with hypoventilation, mouth breathing, or low tidal volumes that lead to low flow rates through the nasal cannula, causing a relatively low end-tidal CO_2 reading.[19,20,30] Alterations in the cardiorespiratory status of the patient also affect the correlation between $PetCO_2$ and $PaCO_2$ levels.[31,32] By applying side-stream capnography in spontaneous breathing preterm and term infants, Tirosh et al[31] demonstrated that the distribution of end-tidal CO_2 wave patterns among preterm infants was different from that of term infants, regardless of gestational age. The inspiration duration was correlated

with the respiratory rate only in preterm infants. This study suggested that although alveolar pathology may be prevalent in preterm infants, it could to a certain degree be disregarded by solely using side-stream capnography.[33] Aliwalas et al[34] found that in intubated neonates, there was a moderate agreement between noninvasive $PetCO_2$ monitoring methods and $PaCO_2$ among preterm infants, but scattered with a wide variation data range. They recommended that noninvasive monitoring methods could not be substituted for $PaCO_2$ analysis in preterm infants $\leq$28 weeks' gestation during the first 24 postnatal hours in intubated neonates; however, we did not see such a wide variation except for one case in our nonintubated infants (Figures 1A and 2A). Tingay et al[35] showed that $PetCO_2$ correlated strongly with $PaCO_2$ and transcutaneous CO_2 in intubated neonates; however, $PetCO_2$ might underestimate $PaCO_2$ at a clinically unacceptable level and was not reliable during neonatal transport. Small tidal volume, higher respiratory rates, and shorter expiratory time in neonates may all contribute to the deficiency in the true alveolar gas measurement, reflecting the wide variation of measured values.[34,35]

Capnometry has been reported to be more accurate for patients without respiratory disease than for those with respiratory compromise. Severity of respiratory disease was reported to affect the accuracy of capnometry in several studies. The more severe the ventilation-perfusion mismatch, the higher the difference between $PetCO_2$ and $PaCO_2$. However, different results had been reported by previous studies.[31,36–39] Using a lung injury animal model constructed by meconium installation, Hopper et al[40] demonstrated that the correlation between $PetCO_2$ and $PaCO_2$ was reduced from 0.94 to 0.80, thus increasing the bias value from 4.23 ± 4.95 mmHg to 20.2 ± 15.1 mmHg. In this study, we found that the $PetCO_2$ bias in patients with respiratory disease was higher than those in patients without respiratory disease (2.4 ± 6.0 mmHg *vs.* 1.2 ± 4.8 mmHg). Although it is statistically significant, most of the distribution values of the $PetCO_2$ bias were within the limits of agreement by the Bland-Altman method.[23,24] An excellent correlation between $PetCO_2$ and $PaCO_2$ among the patients with respiratory disease was still observed.

Despite the concerns listed above, we found that capnometry via nasal cannula may serve as an effective adjunct method for tracing the trends and monitoring the nonintubated neonates for abnormal arterial CO_2 values. Measurement by the same medical professional may contribute to a better precision in noninvasive $PetCO_2$ monitoring, as revealed in our previous study.[15] The respiratory therapist had no difficulty in maintaining the position of the cannula or obtaining a proper waveform in the study. To minimize the impact of these limiting factors, noninvasive monitoring methods for end-tidal CO_2 may help in reducing the necessity of the use of indwelling arterial catheters and the incidence caused by repeated phlebotomy by withdrawing arterial blood samples, avoiding the thermal injury to the infant's fragile skin by transcutaneous probes, and reducing the medical costs in caring for the nonintubated neonates. With this technique, management decisions may also be made at the bedside in real time without laboratory delays, thus preventing possible fluctuations of blood $PaCO_2$ and their associated long term morbidities.[5–9,19,20]

5. Conclusions

We demonstrated that the end-tidal CO_2 measurement via nasal cannula by side-stream capnometry could be easily performed at the bedside and provide an accurate and noninvasive estimation of $PaCO_2$ in nonintubated term and preterm neonates.

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